gradual improvement in swallowing and had no further pain when she was discharged on June 20, 1976.

Discussion

Five cases of esophageal ulceration associated with potassium chloride therapy have been reported in the literature. This is the sixth reported case. These six patients and the five additional patients in whom esophageal stricture developed secondary to potassium chloride therapy ranged in age from 33 to 66 years. Nine were women and two were men. Ten of these patients had taken Slow-K. The dosage, when stated, ranged from 1,200 to 3,600 mg per day. The duration of therapy in these patients is not always clearly stated in the case reports but would appear to range from six days (in the present case) to several months of therapy.

A probable predisposing factor in 9 of the 11 cases appeared to be esophageal compression secondary to left atrial enlargement. In four of the patients esophageal ulceration developed[5-8] and in five esophageal stricture developed following cardiac surgical operation.[8,9] In the other two cases of esophageal ulceration, including the present case, cardiac surgical procedures had not been done. The present patient had left ventricular enlargement and cardiomyopathy.

Compression of the esophagus due to cardiac enlargement may result in stasis and dilatation of the esophagus. Clinical and experimental evidence indicates that the local effect of the hypertonic potassium chloride combined with a relative vascular insufficiency is associated with ulceration in the small bowel.[2,10]

Esophageal ulceration secondary to the administration of wax-matrix potassium chloride or noncoated potassium chloride tablets is a potentially serious complication. Death has resulted in three cases. In two patients, cause of death was hemorrhage.[4,8] The other death was attributed to sepsis related to the septic process in and around the esophageal ulcer.[7] Two other patients required feeding via a jejunostomy and later died.[8]

Slow-K induced esophageal ulceration is a potentially serious complication that may develop in patients with esophageal compression. Patients with cardiac enlargement which may result in esophageal compression should not be given potassium chloride tablets. These tablets should also be avoided in patients with esophageal compression due to other causes.

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Vasculitis Associated With Propylthiouracil

Evidence for Immune Complex Pathogenesis and Response to Therapy

WILLIAM R. GRISWOLD, MD
STANLEY A. MENDOZA, MD
La Jolla, California

WILLIAM JOHNSTON, MD
LCDR STEVEN NICHOLS, MC, USNR
San Diego

PROPYLTHIOURACIL - INDUCED VASCULITIS has been reported previously.[1-6] McCormick[1] established the hypersensitivity nature of the syndrome by showing that the disease recurred when the drug was reintroduced. Inflammatory changes in blood vessels and of skin, liver, central nervous system, pancreas and kidney have been described.

From the Department of Pediatrics, University of California, San Diego, School of Medicine, La Jolla, and Clinical Investigative Center, Naval Regional Medical Center, San Diego.

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Reprint requests to: William R. Griswold, MD, Pediatric Nephrology Division, Dept. of Pediatrics, M8146, UC, San Diego, School of Medicine, La Jolla, CA 92093.

Leukopenia,[3] rash, nephritis, arthritis, disseminated intravascular clotting[2] and positive antinuclear antibody[5] have also been observed.

We recently treated a patient with this syndrome, and report the results of immunologic studies and the response to therapy.

Immunofluorescence studies on skin and kidney were carried out using fluorescein conjugated monospecific antisera to IgA, IgM, IgG, C3 and fibrinogen (Meloy Labs). Cryoglobulins were isolated and characterized as previously described.[7]

Report of a Case

A 14-year-old white girl was admitted to Naval Regional Medical Center, San Diego, for evaluation of malaise, fevers and dark-colored urine. She had been well until 18 months before admission when a goiter developed in association with weight loss and lethargy. Laboratory tests showed a thyroxine (T4) value of 14 μg per dl (normal radioimmunoassay, 4.5 to 11.5 μg per dl). She was treated with propylthiouracil, 400 mg per day, and propranolol. Over the next several months the symptoms disappeared and the thyroid gland became smaller. Propranolol was discontinued after two months, but propylthiouracil was continued with no reduction in dosage until admission.

Menarche had occurred at age 12 and menstrual periods had been regular; however, two to three months before admission amenorrhea developed. At about the same time, malaise, low-grade fevers, gingivostomatitis, weakness and weight loss were noted. The urine had been dark red-brown in color for four weeks before admission.

Past medical history was unremarkable. There was no family history of thyroid or collagen vascular disease. On physical examination, body temperature was 39.4°C (103°F); blood pressure, 102/66 mm of mercury; pulse rate, 105 beats per minute; respiratory rate, 21 per minute; height, 66 inches; weight 116 pounds. There was a perforation in the right tympanic membrane. The thyroid gland was diffusely enlarged. Spleen tip was palpable 2 to 3 cm below the left costal margin. The hematocrit reading was 18 percent; hemoglobin, 6.1 grams per dl, and leukocyte count, 1,800 per cu mm, with 12 percent polymorphonuclear cells, 17 percent bands, 64 percent lymphocytes, 5 percent monocytes, 2 percent eosinophils. Platelet count was 200,000 per cu mm, and reticulocyte count was 0.8 percent. Sedimentation rate was 115 mm per hour. Prothrombin time was 13.5 seconds (control 12). Partial thromboplastin time was 32 seconds (control 26 seconds). Total protein was 7.5 grams per dl; creatinine, 1.5 mg per dl; blood urea nitrogen, 21 mg per dl, and serum glutamic pyruvic transaminase, 18. T4 was 6.7 μg per dl (normal 4.5 to 11.5 μg per dl). Analysis of urine showed pH 6.0, protein 4+, glucose negative, hemoglobin moderate. Microscopic analysis showed red blood cells too numerous to count and many red blood cell casts. Urine protein excretion was 1.1 grams per 24 hours. Hepatitis B antigen (by radioimmunoassay), rheumatoid factor, antistreptolysin O, Veneral Disease Research Laboratories and mononucleosis spot

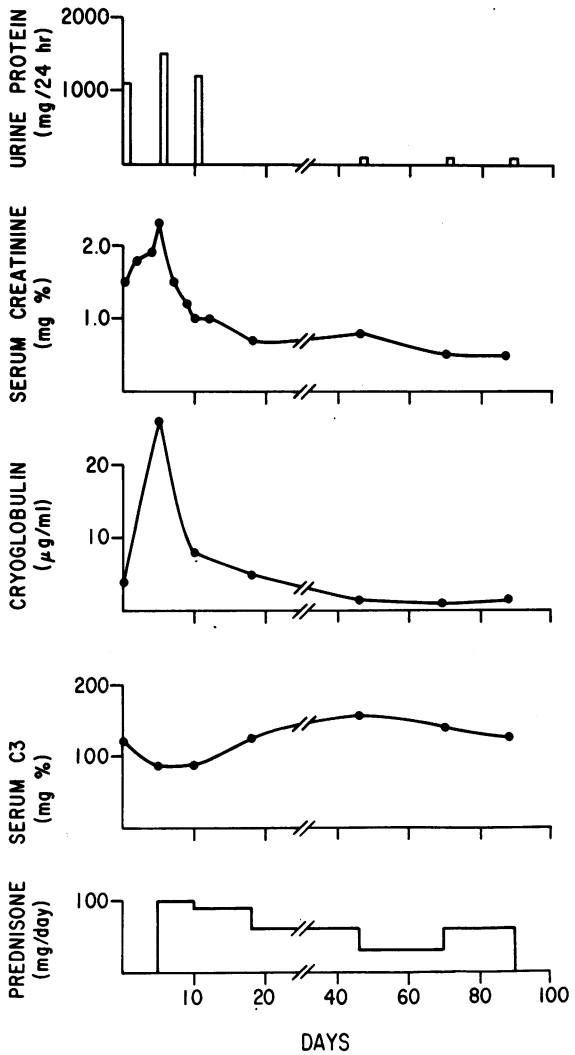

Figure 1.—The response to prednisone therapy. Cryoglobulin is expressed in micrograms of cold insoluble IgG per ml of serum.

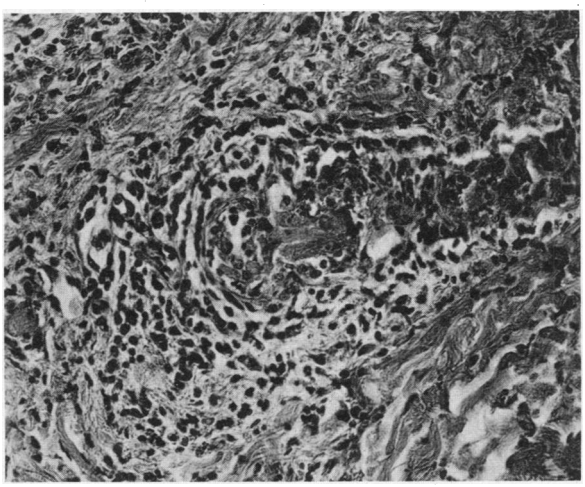

Figure 2.—Representative dermal vessel showing pronounced infiltration with inflammatory cells.

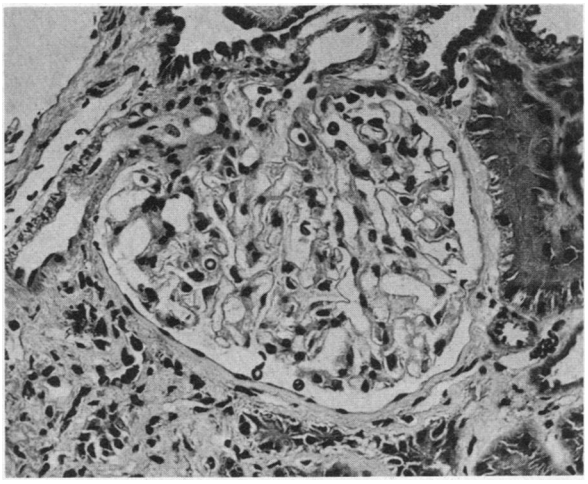

Figure 3.—Representative glomerulus in kidney biopsy specimen taken one week after onset of therapy.

studies were negative. Blood cultures were negative. Throat cultures were negative for β hemolytic streptococci. Antinuclear antibody, LE cell preparation and antithyroglobulin antibody were negative. The following complement studies were done: C3 was 131 mg per dl (normal 90 to 150 mg per dl), C4 was 33 mg per dl (normal 20 to 60 mg per dl), C5 was 11 mg per dl (normal 9 to 13 mg per dl) and total hemolytic complement (CH-50) of 82 units (normal 58 to 103). Quantitative immunoglobulins were as follows: IgG, 2,409 mg per dl (normal 408 to 1,788); IgA, 467 mg per dl (normal 56 to 479), and IgM, 333 mg per dl (normal 50 to 391). A bone marrow biopsy study showed a moderately hypercellular marrow with moderately decreased granulopoiesis and mildly increased erythropoiesis.

Propylthiouracil administration was stopped on admission to the hospital. Over the next five days arthralgias, weakness in the shoulders and trunk, and a maculopapular eruption of purple color covering the legs, forearms, left ear and the dorsum of both feet developed. Reddish-purple raised lesions on the fingers were also noted.

During that time the serum creatinine concentration rose to 2.3 mg per dl, platelet count fell to 56,000 per cu mm, and partial thromboplastin time rose to 45 seconds (control 29 seconds). Fragmented red blood cells were observed in the peripheral blood smear. Serum creatinine phosphokinase rose to 351 and aldolase to 15. A cryoglobulin was isolated from the serum; repeat serum C3 complement was 87 mg per dl (normal 90 to 150). Skin biopsy specimens of lesions on the hand and trunk showed necrotizing vasculitis.

Treatment with prednisone, 100 mg per day, was begun. The patient's condition improved rapidly (Figure 1). Platelet count, partial thromboplastin time and aldolase values became normal in one to two weeks. Hemoglobin became normal in one month. Cryoglobulins disappeared after one month. Administration of steroids was stopped after 90 days of therapy.

The patient has been followed for two years. She is euthyroid, asymptomatic and receiving no medication. Creatinine clearance, 24-hour urine protein, T4 and complete blood count are normal.

Light histology. Skin biopsy specimens taken before steroid therapy showed pronounced perivascular infiltration with lymphocytes, plasma cells and polymorphonuclear leukocytes. Many vessels contained thrombi. Some vessels were frankly necrotic (Figure 2).

A kidney biopsy specimen obtained one week after initiation of steroid therapy contained seven glomeruli. Normal glomeruli (Figure 3), tubules and interstitium were observed. The serum creatinine value at time of biopsy was 1 mg per dl.

Immunofluorescence studies. In skin, deposits of IgG, IgA, IgM and fibrinogen were noted in the walls of the dermal vessels (Figure 4). Albumin control was negative. In the kidney, granular deposits of IgG, IgA, IgM and C3 were observed in the glomeruli (Figure 5). Faint deposits of fibrin were also observed.

Cryoglobulins. A cryoglobulin was isolated from the serum on day 5. It contained IgG, 23.6 μg per ml of serum (normal less than 5 μg per ml); IgM, 31.8 μg per ml of serum (normal less than 10 μg per ml), and IgA, 3.4 μg per ml

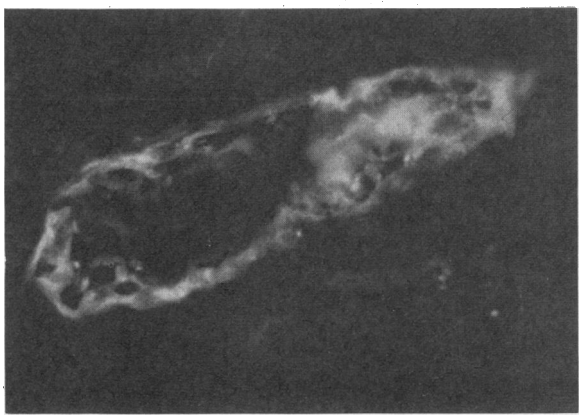

Figure 4.—Deposit of IgM in wall of a dermal vessel.

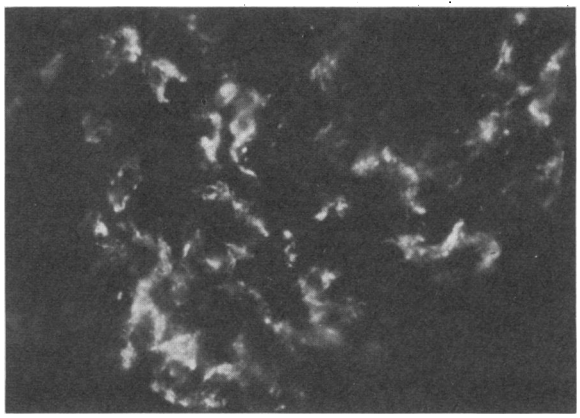

Figure 5.—Deposits of IgA in glomerulus.

of serum (normal, less than 0.5 μg per ml). C3 complement and fibrinogen were not detected in the cryoglobulin.

Discussion

Vasculitis caused by propylthiouracil is a well recognized clinical syndrome. Clinical features include rash, arthritis, leukopenia and anemia.[4] Myositis, observed in this patient, has not been to our knowledge previously reported. Positive antinuclear antibody tests with titers up to 1:160 have been observed in about half of the reported patients. Antileukocyte antibody[6] and disseminated intravascular clotting[2] have been noted. The clinical features of the present case fit the syndrome well and a search for other causes of vasculitis in this patient was unrewarding. Rechallenge with propylthiouracil has produced recurrence of the syndrome and death in other patients and could not be justified in this patient. This patient received a large dose of propylthiouracil for a long period. This may have been an added risk factor for development of the syndrome.

The pathogenesis of vasculitis due to propylthiouracil is not well understood. In the present case the finding of granular deposits of immunoglobulin and complement in the glomerulus and the walls of dermal vessels suggests that the vasculitis is caused by circulating immune complexes. The presence of mixed cryoglobulins, a finding often associated with immune complex disease, adds further support for this hypothesis. These findings have not been previously reported in this syndrome. The nature of the immune complexes is unknown. The drug induces autoimmune phenomena which could result in immune complex formation. Also the drug may act as a hapten, attaching to cell membranes or serum proteins and stimulating antibody production.

The response to steroid therapy in this patient was dramatic. Rash, arthritis, nephritis, thrombocytopenia and cryoglobulinemia, which had worsened before treatment, improved rapidly following initiation of prednisone therapy. Use of steroids may be indicated in other patients with propylthiouracil associated with vasculitis, especially if there is severe involvement of vital organ systems.

Summary

Biopsy specimens from the skin of a patient with vasculitis secondary to propylthiouracil showed necrotizing vasculitis of small blood vessels with intracapillary thrombi on light microscopy and immune deposits in the vessel walls on immunofluorescence. Renal biopsy specimens showed relatively normal glomeruli on light microscopy and granular deposits of immunoglobulin and complement in glomeruli on immunofluorescence. Mixed cryoglobulins were isolated from the serum. The illness responded promptly to treatment with prednisone. These studies support the hypothesis that vasculitis secondary to propylthiouracil is an immune complex disease.

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